

**Biomedical Investigations with Laser-Polarized
Noble Gas Magnetic Resonance**

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Final Technical Report

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PRINCIPAL INVESTIGATOR

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Background and specific aims

We pursued advanced technology development of laser-polarized noble gas nuclear magnetic resonance (NMR) as a novel biomedical imaging tool for ground-based and eventually space-based application. This new multidisciplinary technology enables high-resolution gas-space magnetic resonance imaging (MRI)—e.g., of lung ventilation—as well as studies of tissue perfusion. In addition, laser-polarized noble gases (^3He and ^{129}Xe) do not require a large magnetic field for sensitive detection, opening the door to practical MRI at very low magnetic fields with an open, lightweight, and low-power device. We pursued two technology development specific aims:

- (i) development of low-field (< 0.01 T) noble gas MRI of humans; and
- (ii) development of functional MRI of the lung using laser-polarized noble gas and related techniques.

Accomplishments during grant period

Development of an open human-scale low-field MRI system

A current subject of much debate in the lung physiology community concerns the role of gravitational effects on lung inhalation and function, including the role of gravity in fundamental cardiopulmonary physiology [J. West et al., *Physiologist*. **25**, S21 (1982)]. The recent advances in spin-exchange optical pumping have made laser-polarized noble gas MRI a powerful method for studying lung structure and function. Nevertheless, in conventional MRI systems, patients are restricted to lying in a horizontal position. However, as the laser-polarization is produced without the aid of a large applied magnetic field, we can benefit from a novel magnet design that does not restrict the patient, while still permitting high-quality laser-polarized gas MRI. During the grant period we developed an open-access human-scale imager to operate at low magnetic fields (~ 50 G = 0.005 T), and to allow the orientation of the subject in a 2D plane.

The basic components of the open-access human scale MRI system include a B_0 field of 20 – 70 Gauss, created by two pairs of Helmholtz coils. Custom-designed planar gradients allow complete orientation of subjects in a plane ~ 75 cm wide. Large B_1 coils for human imaging have been built, and are shown in Fig. 1 in place in the imager. Fig. 2 shows a 2-D ^1H image of a large tub of water with dimensions similar to human

lungs, and resolution comparable to human scanners. Fig. 3 shows a 2-D image of a Tedlar bag that has been filled with laser polarized ^3He , transferred from a large-volume ^3He polarizer outside the magnet room.

The results with phantoms indicate the potential for MRI experiments at low field strengths in a large, open-access system, despite low-field limitations of narrow-bandwidth RF coils, and gradient pulses that are not necessarily small compared to the applied field. Further system optimization and human inhalation studies are planned for the follow-on NASA grant for this project.

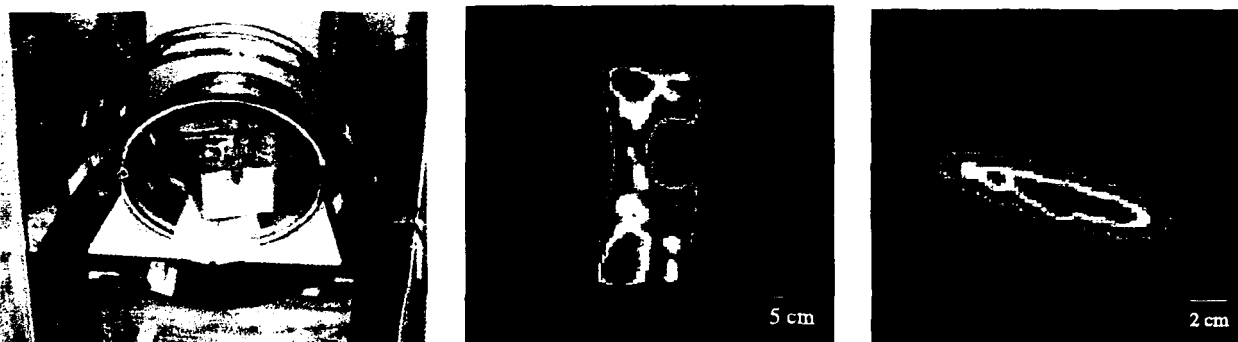


Fig. 1 (left) Large RF coils for human imaging at kHz frequencies, containing small ^3He phantoms. **Fig. 2 (center)** ^1H image of a large tub of water containing a structural object acquired at 30 G (127 kHz) using a spin echo sequence in ~ 4 hours. **Fig. 3 (right)** Image of a plastic gas transfer bag containing laser-polarized ^3He , acquired at 39 G (127 kHz) using a gradient echo sequence with ~ 5 degree flip-angles, acquired in ~ 20 seconds.

Development of gas diffusion NMR as a probe of acinar structure and connectivity

We performed a systematic study of xenon gas diffusion in random packs of mono-sized glass beads, serving as a model system for the lung's acinar structure. NMR is a commonly used, non-invasive probe of *liquid*-saturated porous materials. The restricted diffusion of water molecules can provide a wealth of information including the pore surface-area-to-volume ratio (S/V_p) and the average pore size in model systems. During the grant period we demonstrated that gas diffusion NMR can be a powerful probe of porous media. The spin 1/2 noble gases (^3He and ^{129}Xe) are particularly well suited for such studies, given their rapid diffusion, inert nature, low surface interactions which reduce surface T_1 effects, and the ability to tailor the diffusion coefficient by altering the gas pressure in the sample.

The enhanced signal due to the noble gas laser-polarization process has enabled measurements of noble gas diffusion in the lung. However, attempts to link reduced observed diffusion coefficients to structural detail in the lung have often overlooked effects that are known from porous media study to influence such results. Hence we systematically studied the effects of diffusion by spins over distances on the order of the pore dimensions during the diffusion encoding gradient pulses on measured short-time diffusion coefficients, and the ability to determine the tortuosity, a parameter that describes pore connectivity.

Fig. 4 shows the measured time-dependent diffusion coefficients $D(t)$, of thermally-polarized xenon gas, and water, in a pack of 0.5 mm glass beads, normalized to the free diffusion coefficient, D_0 . Indicated on the figure are the theoretical relationships for the sample's S/V_p (valid at short diffusion times) and tortuosity (the asymptote at long times). It can be seen that at short times, the xenon $D(t)/D_0$ data deviates from the expected relationships, however this effect is reduced as the pressure of the gas is increased. Water $D(t)/D_0$ unambiguously lies on the short time limit.

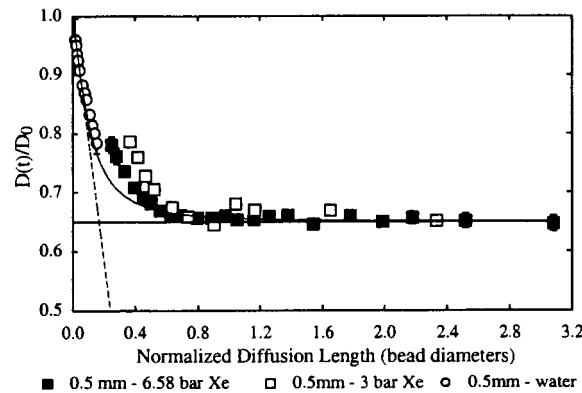


Fig. 4 $D(t)/D_0$ in a sample of 0.5 mm diameter glass beads. ^{129}Xe $D(t)$ was measured at ~ 6 bar (black squares) and 3 bar gas pressure (white squares). Water $D(t)$ data is shown in white circles. $D(t)/D_0$ is plotted against the normalized diffusion length, $b^{-1}\sqrt{D_0 t}$, where b is the bead diameter. The short- t (S/V_p) and long- t (tortuosity) limits for $D(t)/D_0$ are shown by the dashed and solid lines respectively. The curved line extrapolates the long and short- t limits to give an indication of medium- t behavior.

The power of gas diffusion NMR is the ability to derive long-length scale structural information from the asymptotic limit. The concept of tortuosity to describe pore connectivity in rocks could also be a useful parameter to describe the alveolar spaces in lung tissue. However, measurements of $D(t)/D_0$ in small pore volumes at low

gas pressures can often be misleading. At these pressures (a few bar) the gases can easily diffuse across the pore or alveolar dimensions during the application of the gradient pulses, violating the Narrow Pulse Approximation of the PGSE method. Such significant diffusion distances will also tend to reduce the effectiveness of background gradient correction in sequences where this is attempted. The data clearly shows the effect on $D(t)/D_0$ as a result of changing D_0 , by first increasing the gas pressure, and then by changing the observation spin to water. Such effects in the lung will seriously influence $D(t)/D_0$ measurements, resulting in misleading structural information if airspace dimensions are simply concluded from the observed $D(t)/D_0$ data.

Development of xenon gas-tissue exchange NMR as a probe of alveolar S/V

We developed a novel technique for monitoring the exchange of laser-polarized ^{129}Xe between the gas and dissolved phases. When applied to the lung, this technique may provide the first non-invasive measure of the surface-area-to-volume ratio (S/V) of lung alveoli, and as such may have enormous impact on both clinical care and basic physiological research. Alveolar S/V is a critical parameter in the exchange of gas between respiration air and pulmonary blood, the primary function of the lung.

During the grant period, we performed demonstration experiments on a model system: samples of a porous high-density polyethylene polymer rod manufactured by POREX, Inc. (materials commonly used in filtering, wicking, etc.). A series of observed NMR spectra showing the gas-phase signal and the increasing dissolved-phase xenon signal as a function of exchange time is shown in Fig. 5. The dissolved-phase signal recovery data was corrected for RF depletion and T_1 relaxation of laser-polarized ^{129}Xe gas in the pores, giving the normalized xenon exchange signal, which is plotted in Fig. 6 for four different POREX samples. We performed independent measurements of S/V for each POREX sample using optical confocal microscopy, a well-established technique that requires destructive sectioning of the sample. We found reasonable agreement between the NMR and optical measurements of S/V and the related parameter L_m , the mean linear separation between polymer/gas interfaces.

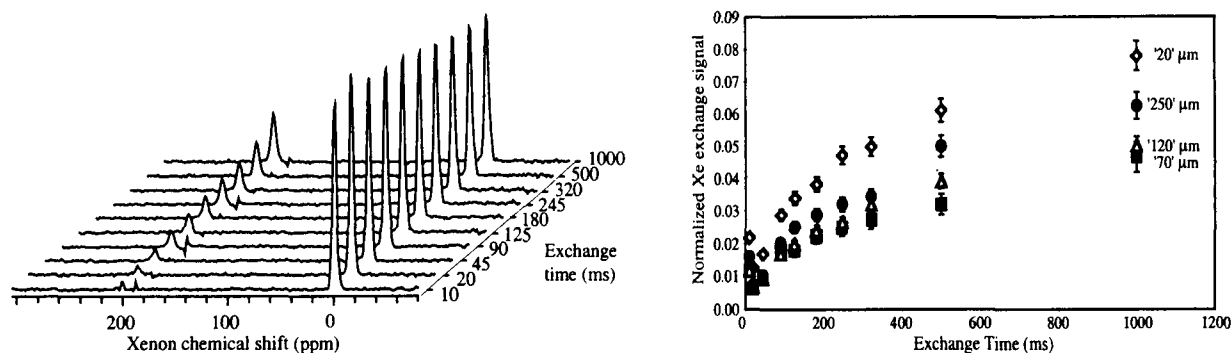


Fig. 5 (left) Stacked plot of NMR spectra showing laser-polarized xenon gas in the pores of the porous polyethylene (POREX) rods at 0 ppm, and the dissolved phase xenon signal at 200 ppm, which increases as a function of interphase-exchange time. **Fig. 6 (right)** Measured recovery due to interphase exchange of the NMR signal from laser-polarized ^{129}Xe dissolved in four POREX polymer rods, which are identified by the manufacturer's nominal quoted pore sizes.

Development of lung blood volume MRI

We developed the first NMR technique to measure and image regional blood volume (RBV) in lung tissue. During the grant period we quantitatively verified the NMR technique in a dialysis canister phantom (a model system with similar properties to lung tissue); and used this technique successfully in RBV measurements in *ex vivo* rabbit lungs. We found our NMR method to be in good agreement with an independent measurement of the "intravascular" volume of the dialysis canister. We also found that the NMR technique determined the microvascular RBV in an unfixed excised rabbit lung in good agreement with previously measured values obtained by microscopic examination of fixed specimens.

Relevant journal papers during grant period

Applications of controlled-flow laser-polarized xenon gas to porous and granular media study.

R.W. Mair, R. Wang, M.S. Rosen, D. Candela, D.G. Cory, and R.L. Walsworth, *Magnetic Resonance Imaging*, **21**, 287 (2003), cond-mat/0211180.

Diffusion NMR Methods Applied to Xenon Gas for Materials Study.

R.W. Mair, M.S. Rosen, R. Wang, D.G. Cory, and R.L. Walsworth, *Magnetic Resonance in Chemistry* **40**, S29 (2002).

The Narrow Pulse Approximation and Long Length Scale Determination in Xenon Gas Diffusion NMR Studies of Model Porous Media.

R.W. Mair, P.N. Sen, M.D. Hürlimann, S. Patz, D.G. Cory, and R.L. Walsworth, *Journal of Magnetic Resonance* **156**, 202 (2002).

Novel MRI Applications of Laser-Polarized Noble Gases.

R.W. Mair and R.L. Walsworth, *Applied Magnetic Resonance* **22**, 159 (2002).

Measuring surface-area-to-volume ratios in soft porous materials using laser-polarized xenon interphase exchange nuclear magnetic resonance.

J.P. Butler, R.W. Mair, D. Hoffmann, M.I. Hrovat, R.A. Rogers, G.P. Topulos, R.L. Walsworth, and S. Patz, *Journal of Physics: Condensed Matter* **14**, L297 (2002).

Tortuosity measurement and the effects of finite pulse widths on xenon gas diffusion NMR studies of porous media.

R.W. Mair, M.D. Hürlimann, P.N. Sen, L.M. Schwartz, S. Patz, and R. L. Walsworth, *Magnetic Resonance Imaging* **19**, 345 (2001).

Measurement of persistence in 1-D diffusion.

G.P. Wong, R.W. Mair, R.L. Walsworth, and D.G. Cory, *Physical Review Letters* **86**, 4156 (2001).

Peer reviewed conference proceedings during grant period

Design and Testing an Open, Human MRI System for Orientational Lung Study.

F.W. Hersman, M.I. Hrovat, R.W. Mair, I. Muradyan, S. Patz, M.S. Rosen, I. Ruset, L.L. Tsai, R.L. Walsworth, *Proceedings of the Eleventh Scientific Meeting of the International Society for Magnetic Resonance in Medicine*, Toronto, Canada, 2003.

Velocity Imaging and Spectroscopy of Xenon Gas Flow.

R.W. Mair, R. Wang, M.S. Rosen, D.G. Cory, R.L. Walsworth, *Proceedings of the Eleventh Scientific Meeting of the International Society for Magnetic Resonance in Medicine*, Toronto, Canada, 2003.

Signal Correction for Narrow-Bandwidth Coils.

M.I. Hrovat, F.W. Hersman, S. Patz, R.W. Mair, R.L. Walsworth, *Proceedings of the Eleventh Scientific Meeting of the International Society for Magnetic Resonance in Medicine*, Toronto, Canada, 2003.

Applications of Controlled-Flow Laser-Polarized Xe Gas to Porous and Granular Media Study.

R. W. Mair, R.. Wang, M. S. Rosen, D. Candela, D. G. Cory and R. L. Walsworth,
Sixth International Meeting on Recent Advances in MR Applications to Porous
Media, Ulm, Germany, 2002.

Design and Construction of an Open Human-Scale Low-Field Imaging System.

F.W. Hersman, I. Ruset, S. Patz, M.I. Hrovat, R.W. Mair, M.S. Rosen, R.L.
Walsworth, Proceedings of the Tenth Scientific Meeting of the International Society
for Magnetic Resonance in Medicine, Honolulu, HI, 2002, p. 836.

Accurate Quantification of Fractional Blood Volume in Lung Tissue.

G.P. Topulos, S. Patz, J.P. Butler, L.L. Tsai, R.W. Mair, M.S. Rosen, R.L. Walsworth,
Proceedings of the Tenth Scientific Meeting of the International Society for Magnetic
Resonance in Medicine, Honolulu, HI, 2002, p. 1983.

Narrow Pulse Effects and Tortuosity Studies in Porous Media using Xenon Diffusion NMR.

R.W. Mair, P.N. Sen, M.D. Hurlimann, S. Patz, D.G. Cory, R.L. Walsworth,
Proceedings of the Tenth Scientific Meeting of the International Society for Magnetic
Resonance in Medicine, Honolulu, HI, 2002, p. 2007.

Using ^{129}Xe gas exchange measurements to determine surface area to volume ratios in porous media.

R.W. Mair, S. Patz, J.P. Butler, D. Hoffmann, G.P. Topulos, R.L. Walsworth,
Proceedings of the Eighth Scientific Meeting of the International Society for
Magnetic Resonance in Medicine, Denver, CO, 2000, p. 2190.